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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/579,420	05/25/2000	Michael Klagsbrun	701039-47875-C	7567

7590 02/12/2002

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EXAMINER	
NICKOL, GARY B	
ART UNIT	**PAPER NUMBER**
1642	10

DATE MAILED: 02/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/579,420	KLAGSBRUN ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 7-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed on January 15, 2002 (Paper No. 9) to the restriction requirement of October 2, 2001 has been received. Applicant has elected Group I, claims 1, 4-5 for examination without traverse. Claims 2-3, and 7-14 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b), as being drawn to non-elected inventions. Thus, claims 1, 4-6 are pending and are currently under examination.

Specification

The specification is objected to for the following reason: The specification on page 1 should be amended to reflect the priority status of the present application, for example:

This application is a continuation of PCT/US98/26103, filed December 9, 1998 which claims benefit to US Provisional Application 60/069,687, filed December 12, 1997, now abandoned and US Provisional Application 60/069,155, filed December 9, 1997, now abandoned.

The specification is further objected to on page 10, lines 1-11 (see Figure 5B) for improper disclosure of amino acid sequences without a respective sequence identifier, i.e. a SEQ ID NOs:. Figure 5B contains an amino acid sequence without a sequence identifier. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form

(CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d).

Claim Objections

Claims 4-6 are objected to because claim 4 is dependent from nonelected claims (i.e. claims 2 and 3). The objection can be obviated by amending the claims to depend from the elected claims such as claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising a portion of SEQ ID NO. 1 having VEGF antagonist activity wherein said portion includes amino acids 22-44 of SEQ ID NO:1, does not reasonably provide enablement for an isolated polypeptide having a portion of SEQ ID NO:1 having VEGF antagonist activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to an isolated polypeptide having a portion of SEQ ID NO:1 having VEGF antagonist activity (Claim 1); a pharmaceutical composition comprising a polypeptide of claim 1 and a pharmaceutically acceptable carrier (Claim 4), wherein the carrier is acceptable for topical application to the skin (Claim 5) or application to the eye (Claim 6).

Thus, the recited "portions" of the claimed polypeptide having VEGF antagonist activity include a whole universe of polypeptide derivatives and amino acid fragments with or without the VEGF antagonist activity as claimed.

The specification teaches (page 11, line 23) that the portion has at least a 25% reduction in HUVEC proliferation, more preferably a 50% reduction, even more preferably a 75% reduction, most preferably a 95% reduction. Preferably, the portion has an even number of cysteine residues. The specification further teaches (page 12, line 12+) that derivatives of VEGF antagonist polypeptides are those in which one or more physical, chemical, or biological properties have been altered including, but not limited to, amino acid substitutions, modification, additions or deletions, alterations in the pattern of lipidation, glycosylation or phosphorylation. Finally, with regards to portions of SEQ ID NO:1, the specification teaches (page 27, lines 20-25) several portions of SEQ ID NO:1- including those with a complete loss of VEGF inhibitory

activity. Moreover, the specification teaches that amino acids 22-44 of exon 7 are essential since the results indicated that the inhibitory core is found within amino acids 22-44 of exon 7. Hence, it is clear that all portions of SEQ ID NO:1 do not have VEGF antagonist activity nor would one of skill in the art reasonably expect that all such portions would have VEGF activity.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any and all portions of SEQ ID NO:1 with or without the biological properties of what is claimed, and applicant has not enabled all of these types of modified proteins because it has not been shown that these modified proteins are capable of functioning as VEGF antagonists. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of substituted proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the

disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all portions of SEQ ID NO:1 having VEGF antagonist activity. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as anticipated by Fleurbaaij *et al.* (WO/9606641), March 1996 as evidenced by accession No. AAR94041, attached.

The claim is drawn to an isolated polypeptide having a portion of SEQ ID NO:1 having VEGF antagonist activity.

Fleurbaaij *et al.* teach an isolated polypeptide having a portion of SEQ ID NO:1 (see attached sequence comparison). Although the reference does not specifically teach that the isolated polypeptide has VEGF antagonist activity, the claimed peptide appears to be the same as the prior art . The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. Hence, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fleurbaaij *et al.* (WO/9606641), March 1996.

Fleurbaaij *et al.* teach as set forth above; however, there is no specific teaching of the claimed polypeptide (the portion of SEQ ID NO:1 is equivalent to SEQ ID NO:23 on page 121 of Fleurbaaij *et al.*) with a pharmaceutical carrier including a carrier that is acceptable for topical application to the skin or application to the eye.

Fleurbaaij *et al.* teach (page 67, line 14+) that the conjugates can be used in pharmaceutical compositions to treat VEGF-mediated pathophysiological conditions by targeting to cells that bear VEGF receptors and inhibiting proliferation of or causing death of the cells. Fleurbaaij *et al.* further teach (page 66, lines 7-24) that the conjugates may be prepared with carriers that protect them against rapid elimination from the body, such as time release formulations or coating. These are particularly useful for "applications to the eye". The conjugates may be formulated for local or topical application as well, such as for topical application to the skin and mucous membranes. By definition, Fleurbaaij *et al.* define "conjugate" (page 6) as a molecule that contains at least one VEGF moiety and at least one targeted agent that are linked directly or via a linker and that are produced by chemical coupling methods or by recombinant expression of chimeric DNA molecules to produce fusion proteins. Furthermore, Fleurbaaij *et al.* teach (page 11, line 8) that VEGF includes any combination of peptides encoded by the exons set forth in SEQ ID NOs: 16-24.

Therefore, it would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to make a pharmaceutical composition comprising an isolated polypeptide having a portion of SEQ ID NO:1 having VEGF antagonist activity as taught by Fleurbaaij *et al.* with a pharmaceutically acceptable carrier since clearly Fleurbaaij *et al.* suggest that the conjugates can be used in pharmaceutical compositions to treat VEGF-mediated pathophysiological conditions by targeting to cells that bear VEGF receptors and inhibiting proliferation of or causing death of the cells. Further, it would have been obvious to include carriers acceptable for topical application to the skin or to the eye because Fleurbaaij *et al.* suggest that the conjugates may be prepared with carriers that protect them against rapid elimination from the body, such as time release formulations or coating which are particularly useful for "applications to the eye" as well as for topical application to the skin and mucous membranes.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
February 4, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

CC the treatment or prophylaxis of cancers. The present sequence is
CC used in the course of the invention.
XX
SQ Sequence 44 AA;

Query Match 96.6%; Score 255; DB 20; Length 44;
Best Local Similarity 100.0%; Pred. No. 4.5e-21;
Matches 44; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 PCGPCSERRKHLFVQDPQTCKCSCKNTDSRCKARQLELNERTCR 44
||||||||||||||||||||||||||||||||||||||||||||
Db 1 pcgpcserrkhlfvqdpqtckcsckntdsrckarqlelnertcr 44

RESULT 4
AAR94041
ID AAR94041 standard; Protein; 44 AA.
XX
AC AAR94041;
XX
DT 10-OCT-1996 (first entry)
XX
DE VEGF exon VII.
XX
KW Vascular endothelial growth factor; VEGF; human; conjugate; tumour; iris;
KW proliferation inhibition; VEGF-mediated pathophysiological condition;
KW dermatological disorder; VEGF receptor; vascular proliferation; retina;
KW ophthalmic disorder; hyperproliferating blood vessel; therapy; psoriasis;
KW conjunctiva; vitreous humour; rheumatoid arthritis; skin cancer;
KW varicose veins; gene therapy.
XX
OS Homo sapiens.
XX
PN WO9606641-A1.
XX
PD 07-MAR-1996.
XX
PF 29-AUG-1995; 95WO-US10973.
XX
PR 16-MAY-1995; 95US-0441979.
PR 29-AUG-1994; 94US-0297961.
XX
PA (PRIZ-) PRIZM PHARM INC.
XX
PI Fleurbaaij GA, Freund E, Houston LL, Nova MP, Sosnowski BA;
PI Victor KD;

WPI; 1996-160151/16.
N-PSDB; AAT17749.
XX
PT Vascular endothelial cell growth factor (VEGF) conjugates - having
PT VEGF linked to targeted agent, used for inhibiting proliferation of
PT cells, e.g. for gene therapy
XX
PS Disclosure; Page 121; 193pp; English.
XX
CC AAR94033-R94038, AAR94041, AAR94042 and AAW00582 represent vascular
CC endothelial growth factors (VEGF) exons. This sequence represents exon
CC VII. These sequences were used in VEGF conjugates of the invention. In
CC the conjugates, VEGF (or fragments of it) are linked to a targeted agent
CC (this can be via a linker sequence), so that the conjugate binds to a
CC VEGF receptor. Cys-modified forms of VEGF are particularly suitable for
CC chemical conjugation to linkers and targeted agents. The conjugates are
CC used for inhibiting proliferation of cells bearing VEGF receptors. They
CC can be used for treating a VEGF-mediated pathophysiological condition,
CC including dermatological disorders with underlying vascular
CC proliferation, solid tumours or an ophthalmic disorder of
CC hyperproliferating blood vessels of the retina, iris, conjunctiva or
CC vitreous humour. The conjugates can also be used for treating
CC psoriasis, rheumatoid arthritis, skin cancers and other tumours, or
CC varicose veins. They are also suitable for use in gene therapy.
XX
SQ Sequence 44 AA;

Query Match 94.7%; Score 250; DB 17; Length 44;
Best Local Similarity 100.0%; Pred. No. 1.6e-20;
Matches 43; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 PCGPCSERRKHLFVQDPQTCKCSCKNTDSRCKARQLELNERTC 43
|||||||||||||||||||||||||||||||||||||||||||
Db 1 pcgpcserrkhlfvqdpqtckcsckntdsrckarqlelnertc 43

RESULT 5
AAB18547
ID AAB18547 standard; peptide; 41 AA.
XX
AC AAB18547;
XX
DT 15-JAN-2001 (first entry)
XX
DE Immunogenic peptide fragment derived from FGF and/or VEGF.
XX
KW Immunogenic peptide; fibroblast growth factor; FGF; VEGF; cancer;
KW vascular endothelial growth factor; hyperproliferative disorder;
KW haemangioma; solid tumour; blood borne tumour; leukaemia; metastasis;
KW telangiectasia; psoriasis; scleroderma; pyogenic granuloma;
KW myocardial angiogenesis; Crohn's disease; plaque neovascularisation;
KW arteriovenous malformation; corneal disease; rubeosis;
KW neovascular glaucoma; diabetic retinopathy; retrolental fibroplasia;
KW arthritis; diabetic neovascularisation; macular degeneration;
KW wound healing; peptic ulcer; Helicobacter related disease; fracture;
KW keloid; vasculogenesis; hematopoiesis; ovulation; menstruation;
KW placentation; cat scratch fever.
XX
OS Unidentified.
XX
PN WO200053219-A2.
XX
PD 14-SEP-2000.
XX
PF 10-MAR-2000; 2000WO-US06320.
XX
PR 11-MAR-1999; 99US-0266543.
XX
PA (ENTR-) ENTREMED INC.
XX
PI Holaday JW, Ruiz A, Madsen J;
XX
DR WPI; 2000-594263/56.
XX
PT An immunogenic composition useful for treating cancer or
PT hyperproliferative disorders comprises an immunogenic peptide fragment
PT of fibroblast growth factor and/or vascular endothelial growth factor -
XX
PS Claim 13; Page 28; 95pp; English.
XX
CC AAB18542-51 represent immunogenic peptide fragments of fibroblast
CC growth factor (FGF) and/or vascular endothelial growth factor (VEGF).
CC The peptides are used to produce immunogenic compositions. The
CC immunogenic composition is used for treating cancer or
CC hyperproliferative disorders, especially haemangioma, solid tumours,
CC blood borne tumours, leukaemia, metastasis, telangiectasia, psoriasis,
CC scleroderma, pyogenic granuloma, myocardial angiogenesis, Crohn's
CC disease, plaque neovascularisation, arteriovenous malformations,
CC corneal diseases, rubeosis, neovascular glaucoma, diabetic retinopathy,
CC retrolental fibroplasia, arthritis, diabetic neovascularisation, macular
CC degeneration, wound healing, peptic ulcer, Helicobacter related
CC diseases, fractures, keloids, vasculogenesis, hematopoiesis, ovulation,
CC menstruation, placentation and cat scratch fever.
XX
SQ Sequence 41 AA;